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Review Article

Orthostatic Hypotension and Falls in Older Adults: A Systematic Review and Meta-analysis

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A B S T R A C T

Objectives: Orthostatic hypotension is a potential risk factor for falls in older adults, but existing evidence on this relationship is inconclusive. This study addresses the association between orthostatic hypotension and falls.

Design: Systematic review and meta-analysis of the cross-sectional and longitudinal studies assessing the association between orthostatic hypotension and falls, as preregistered in the PROSPERO database (CRD42017060134).

Setting and participants: A literature search was performed on February 20, 2017, in MEDLINE (from 1946), PubMed (from 1966), and EMBASE (from 1947) using the terms *orthostatic hypotension*, *postural hypotension*, and *falls*. References of included studies were screened for other eligible studies. Study selection was performed independently by 2 reviewers using the following inclusion criteria: published in English; mean/median age of the population ≥65 years; blood pressure measurement before and after postural change; and assessment of the association of orthostatic hypotension with falls. The following studies were excluded: conference abstracts, case reports, reviews, and editorials. Data extraction was performed independently by 2 reviewers.

Measures: Unadjusted odds ratios of the association between orthostatic hypotension and falls were used for pooling using a random effects model. Studies were rated as high, moderate, or low quality using the Newcastle-Ottawa Scale.

Results: Out of 5646 studies, 63 studies (51,800 individuals) were included in the systematic review and 50 studies (49,164 individuals) in the meta-analysis. Out of 63 studies, 39 were cross-sectional and 24 were longitudinal. Orthostatic hypotension was positively associated with falls (odds ratio 1.73, 95% confidence interval 1.50-1.99). The result was independent of study population, study design, study quality, orthostatic hypotension definition, and blood pressure measurement method.

Conclusions and implications: Orthostatic hypotension is significantly positively associated with falls in older adults, underpinning the clinical relevance to test for an orthostatic blood pressure drop and highlighting the need to investigate orthostatic hypotension treatment to potentially reduce falls.

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The authors declare no conflicts of interest.

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Orthostatic hypotension (OH) is defined as a blood pressure drop of at least 20 mmHg in systolic blood pressure (SBP) and/or 10 mmHg in diastolic blood pressure within 3 minutes after standing up.[1] OH is prevalent at older age and in individuals with comorbidities such as cardiovascular disease[2] and Parkinson's disease (PD),[3] as this disease often entails dysfunction of the autonomous nervous system.

OH is considered a risk factor for falls, potentially causing falls directly (ie, within seconds) after standing up by decreased brain perfusion and subsequent decreased brain oxygenation.[4] Alternatively, OH might cause falls by indirect mechanisms, such as cerebral white matter lesions.[5] However, studies on the association of OH and falls are inconclusive as some report a positive association[6,7] and others found no association.[8,9] Previous studies summarized existing evidence on the association of OH and falls, but either did not perform a meta-analysis[10–12] or were restricted to prospective studies with available individual patient data, resulting in a low number of included studies, which prevented subgroup analysis, for example, for the study population.[13]

The aim of this study was to systematically review the existing literature and perform a meta-analysis on the association between OH and falls in various populations of older adults aged 65 years or older and to address the influence of study population, study design (ie, cross sectional or longitudinal), study quality, applied OH definition, and blood pressure measurement method. It was hypothesized that OH is positively associated with falls.

Methods

The review protocol was registered at the PROSPERO International prospective register of systematic review (CRD42017060134). This study was performed in accordance with the PRISMA and MOOSE guidelines. A search was performed in MEDLINE (from 1946), PubMed (from 1966), and EMBASE (from 1947) to February 20, 2017, and included the terms *orthostatic hypotension*, *postural hypotension*, and *falls*. The complete search strategy is presented in Supplementary Material 1.

Study Selection

Screening of titles and abstracts and subsequent full-text articles was performed independently by 2 reviewers (A.M. and P.T.S.B.H.). Any disagreements between reviewers were resolved by a third reviewer (E.M.R., C.G.M., or A.B.M.). Studies were eligible if they met the following inclusion criteria: published in English; mean or median age of the included population 65 years or older; blood pressure measurements before and after a postural change; assessment of falls; and assessment of the association of OH with falls. Conference abstracts, case reports, reviews, editorials, and letters to the editor were excluded as these publications do not report original data or do not allow for study quality assessment. Studies were organized and managed using EndNote (version X8.2; Clarivate Analytics, Philadelphia, PA). References of eligible studies were screened for other studies meeting the criteria.

Data Extraction and Study Quality Assessment

The following variables were independently extracted by 2 reviewers (A.M. and P.T.S.B.H.): first author; year of publication; age; sex; study population; study design; type of postural change (eg, active stand or head up tilt); blood pressure measurement method (ie, intermittent or continuous); OH definition; prevalence of OH; odds ratio (OR) of the association of OH and falls; or fall prevalence in the group with and without OH.

The quality of the included studies was assessed independently by 2 authors (A.M. and P.T.S.B.H.) using the 9-point Newcastle-Ottawa Scale (NOS), higher scores indicating lower risk of bias. Studies with NOS scores ranging from 0 to 3, 4 to 6, and 7 to 9 points were considered as low, moderate, and high quality, respectively. The specified NOS for this study is provided in Supplementary Material 2.

Study Selection for Meta-analysis and Data Synthesis

Studies were included in the meta-analysis if an OR was reported or an OR could be reconstructed from reported data on fall prevalence in the group with and without OH. Unadjusted ORs were used rather than adjusted ORs to reduce heterogeneity. If available, continuously measured blood pressure was used rather than intermittently measured blood pressure as continuous blood pressure measurements are more sensitive for the diagnosis of OH.[14] The consensus definition of OH (ie, SBP drop $\geq$20 mmHg or diastolic blood pressure drop $\geq$10 mmHg within 3 minutes after standing up) was used rather than the systolic OH definition (ie, SBP drop $\geq$20 mmHg within 3 minutes after standing up) and the initial OH definition (iOH; ie, SBP drop $\geq$40 mmHg or diastolic blood pressure drop $\geq$20 mmHg within 15 seconds after standing up). Results of active stand tests rather than other types of postural change (eg, head up tilt test) were used, as these most resemble daily life situations.

Meta-analysis

Meta-analyses of studies with an available reported or calculated OR were performed using Review Manager (RevMan, version 5.3, The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen). A random effects model was used because the included studies differed with respect to study population and design. Subgroup analyses were performed for study population (categorized as community-dwelling adults, geriatric outpatients, geriatric inpatients, nursing home residents, patients with PD, and patients with other specific diseases), study design (ie, cross-sectional or longitudinal), study quality (assessed using the NOS), OH definition (ie, consensus OH, systolic OH, iOH, or other OH definition), and blood pressure measurement method (continuous or intermittent), if at least 2 studies were available. Heterogeneity was investigated using the I^2 statistic, with values $<$25%, 25% to 50%, and $>$50% indicating low, moderate, and high heterogeneity, respectively. P values $<$.05 were considered statistically significant. Risk for publication bias was calculated using the Egger test for meta-analyses including at least 10 studies using a significance level of 10%.[15]

Results

Study Selection

Figure 1 shows the PRISMA flow diagram of study identification and selection. Out of 8133 abstracts, 5645 were unique. Of these, 332 were selected for full-text screening, and 63 studies were included in the systematic review. Fifty studies reported an OR or prevalence data, enabling inclusion in the meta-analysis.

Systematic Review

Table 1 lists the study characteristics, results on the association between OH and falls, and study quality of all 63 studies (51,800 individuals). Study populations consisted of community-dwelling adults (17 studies), geriatric outpatients (12 studies), geriatric inpatients (5 studies), nursing home residents (14 studies), patients with PD (8 studies), and patients with specific other diseases (7 studies).

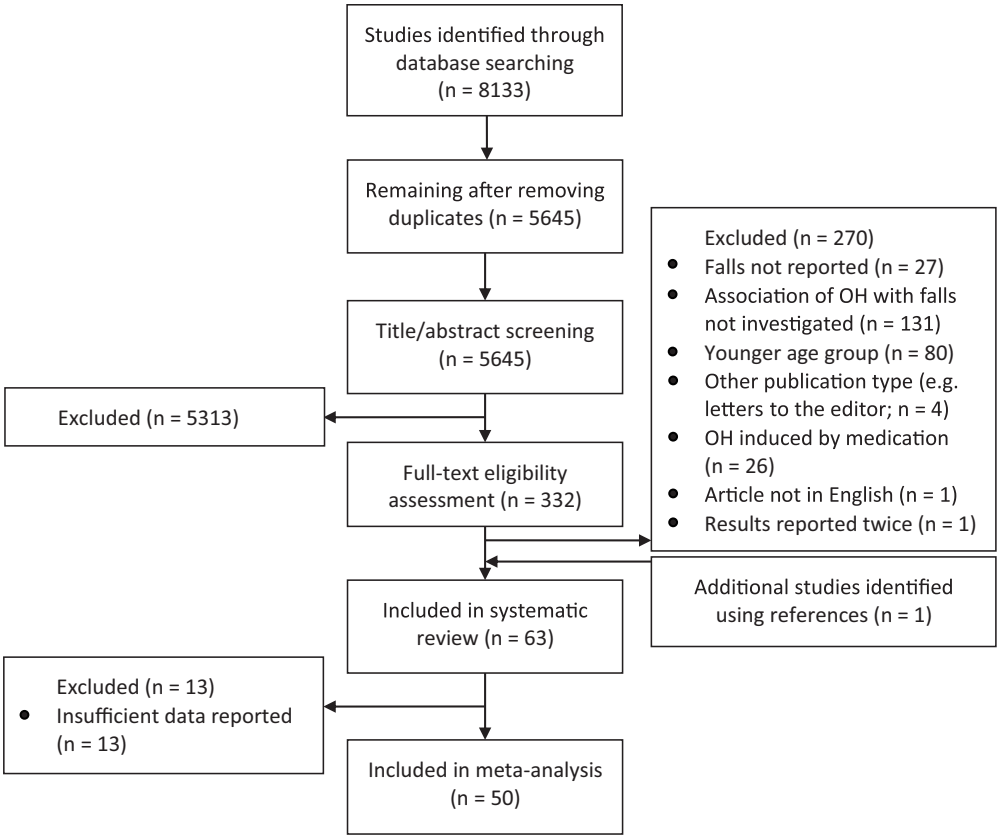

Fig. 1. PRISMA flow diagram of study identification and selection.

Thirty-nine studies were cross-sectional and 24 studies were longitudinal. Seven studies were of high quality, 35 studies of moderate quality, and 21 studies of low quality. Supplementary Material 3 lists the study quality per NOS item. Thirty-eight studies applied the consensus definition of OH, 16 studies used the systolic OH definition, and 9 studies used other definitions or did not report the used definition. The blood pressure measurement method used was intermittent in 36 studies, continuous in 13 studies, and not reported in 14 studies. Twenty-four of the 63 studies reported a positive association of OH and falls, and the other studies reported no association.

Meta-analysis

Figure 2 shows the forest plot of the 50 studies included in the meta-analysis (49,164 individuals). OH was significantly positively associated with falls [OR 1.73, 95% confidence interval (CI) 1.50-1.99; $P < .001$]. Overall heterogeneity was high ($I^2 = 68\%$). Egger test showed no evidence for publication bias ($P = .431$).

Figure 3 shows the subgroup analyses for study population, study design, study quality, OH definition, and blood pressure measurement method. Significant positive associations were found in all subgroups. The OR of the association between OH and falls was highest for patients with PD (OR 2.30, 95% CI 1.53-3.48), longitudinal studies (OR 2.05, 95% CI 1.49-2.80), studies with low quality (OR 1.77, 95% CI 1.36-2.32), studies using the systolic OH definition (OR 1.69, 95% CI 1.02-2.81), and studies using continuous blood pressure measurements (OR 2.35, 95% CI 1.76-3.13) in these respective subgroup analyses. Heterogeneity in all subgroups was moderate or high, except for studies using the continuous blood pressure measurements, which had low heterogeneity.

Discussion

This systematic review and meta-analysis demonstrated a consistent positive association between OH and falls. This is the first study showing independence of this association from study population, study design, study quality, OH definition, and blood pressure measurement method. These results indicate the clinical importance to test for OH in older adults and the need to study if OH interventions reduce falls.

The positive association found between OH and falls was independent of study quality, which, together with the large number of individuals included, supports the robustness of the evidence. Furthermore, the Egger test did not indicate the presence of publication bias.

The association of OH with falls in cross-sectional studies might indicate a potential causal relationship, which could work in both directions. OH might cause an acute drop in cerebral oxygenation because of an impaired cerebral autoregulation, resulting in dizziness and falls.[4] Alternatively, OH might cause brain atrophy, microbleeds, and white matter brain lesions, resulting in falls.[5] OH might also cause falls through impaired muscle microcirculation, as one study found an association of OH with muscle ischemia.[74] Conversely, falls might cause OH by fear of falls, with consequent behavioral changes including lower physical activity, resulting in deconditioning and muscle loss.[75] However, current evidence does not support this, as OH was not found to be associated with physical activity.[27,31,63]

Table 1
Study Characteristics, the Reported Association of OH With Falls (Positive, Negative, or Absent) and Study Quality of the Studies Included in the Systematic Review (n = 63)

First Author, Year of Publication	N	Age, y*	Female, %	Study Design	OH Definition	Postural Change	BP Measurement	Assessment of Falls	Period of Fall Assessment, m	OH, %	Association, +/=/−	NOS	Meta-analysis, +/−
Community-dwelling adults													
Campbell, 1989[16]	761	>70	59.9	L	sOH	AS	I	D	12	31.4	=	5	+
Chang, 2010[17]	1361	72 (5.1)	39.6	Cs	cOH	AS	NR	I/Q	12	30.9	=	5	+
Ensrud, 1992[18]	9704	72 (65-99)	100	Cs	sOH	AS	I	I/Q	12	14.0	=	3	+
Gangavati, 2011[19]	722	78 (5.1)	73.1	L	cOH	AS	I	D	12	6.0	=	7	+
Heitterachi, 2002[20]	70	77 (5.9)	80	L	sOH	HUT	C	I/Q	12	14	+	6	−
Kario, 2001[21]	266	76 (5.0)	46.0	L	sOH−	AS	I	D	12	19.5	=	4	−
Liu, 1995[22]	96	83 (6.0)	82	L	sOH	AS	I	D	12	NR	=	5	−
Lord, 1995[23]	414	74 (6.3)	100	L	sOH	AS	I	I/Q	12	22.6	=	4	−
Mader, 1987[24]	300	70 (56-93)	77.0	Cs	sOH	AS	I	I/Q	12	10.7	=	3	+
McDonald, 2016[25]	79	73 (6.8)	51	L	cOH	AS	C	D	12	81	+	7	+
Menant, 2016[26]	529	80 (4.4)	52.2	L	cOH	HUT	I	D	12	22.1	+	7	+
Romero-Ortuno, 2011[27]	442	72	72.0	Cs	cOH	AS	C	I/Q	6	94.1	=	5	+
Rutan, 1992[28]	4931	>65	56.5	Cs	cOH	AS	I	I/Q	12	16.2	+	5	+
Wong, 2013[29]	520	80 (4.4)	50.8	L	cOH	HUT	I	D	12	22.7	=	6	+
Yu, 2009[30]	1512	71 (6.5)	59.1	Cs	NR	NR	NR	I/Q, MR	NR	21.9	+	2	+
Zhu, 2016[31]	364	75 (64-98)	50.5	Cs	cOH	AS	I	I/Q	12	11.0	=	3	+
Zia, 2015[32]	358	74 (6.5)	67.6	Cs	cOH	AS	I	I/Q	12	22.3	+	5	+
Geriatric outpatients													
Allan, 2009[33]	179	76 (6.2)	40.8	L	cOH	AS	C	D	12	12.5	+	8	-
Aydin, 2017[34]	290	75 (8.7)	59.3	Cs	cOH	AS	I	I/Q	12	37.2	=	4	+
Blumenthal, 1980[35]	100	60-95	70.0	Cs	sOH+	AS	I	I/Q	NR	39.0	+	1	-
Davies, 2001[36]	80	78 (7.3)	20	Cs	sOH	AS	C	I/Q	NR	23	=	5	+
Gaxatte, 2017[7]	833	80 (7.4)	73.1	L	cOH	AS	I	I/Q	6	23.9	+	5	+
Miu, 1997[37]	400	74	58.8	Cs	sOH	AS	I	I/Q	12	22.8	=	2	+
Pasma, 2014[14]	58	81 (7.0)	57	Cs	iOH/cOH	As	C	I/Q	12	57	+	5	+
Press, 2016[9]	571	84 (6.1)	64.1	Cs	cOH	AS	I	I/Q	12	32.2	=	3	+
Saedon, 2016[38]	267	74 (6.6)	68.8	Cs	cOH	AS	C	I/Q	12	69.7	+	5	+
Susman, 1989[39]	100	73 (65-90)	62.0	Cs	sOH	AS	I	I/Q	12	31.0	=	3	+
Van der Velde, 2007[40]	217	77 (5.8)	65.6	Cs	cOH	HUT	C	I/Q	12	59.8	+	4	+
Van der Velde, 2007[41]	211	77 (5.7)	65.3	Cs	cOH	HUT	C	I/Q	12	60.1	+	8	+
Geriatric inpatients													
Chen, 2009[42]	404	68 (16.9)	26.2	L	cOH	NR	I	I/Q	LoS	4.2	+	4	+
Coutaz, 2012[43]	340	81 (8.1)	68.5	L	cOH	AS	I	I/Q	6	51.5	=	4	+
Jodaitis, 2015[44]	285	85 (5.0)	54.0	Cs	cOH	AS	I	I/Q	6	41.0	+	4	+
Passant, 1997[45]	151	75	38.6	L	sOH	AS	I	NR	NR	46.0	=	3	+
Soysal, 2016[46]	407	75 (8.5)	62.9	Cs	cOH	HUT	I	I/Q	12	22.1	+	4	+
Nursing home residents													
Bumin, 2002[47]	33	70 (2.2)	NR	Cs	sOH	StS	I	I/Q	NR	30	=	2	+
Graafmans, 1996[48]	354	83 (6.0)	85.0	L	cOH	AS	NR	D	4	21.0	=	6	+
Gray-Miceli, 2016[49]	47	91 (5.8)	74	Cs	cOH	NR	NR	MR	NR	15	=	3	−
Hall, 2015[50]	510	77 (11.5)	26.9	Cs	sOH	NR	NR	I/Q	6	8.6	=	3	−
Hartog, 2015[51]	290	81 (9.9)	71.0	Cs	cOH	AS	I	I/Q	12	36.6	=	4	+
Hartog, 2017[8]	246	82 (76-87)	70.0	L	cOH	AS	I	Obs	15.6	37.0	=	7	−
Jonsson, 1990[52]	58	86 (5.7)	66	Cs	sOH	AS	C	MR	6	26	=	2	+
Makhlouf, 2000[53]	165	73 (7.6)	62.4	Cs	cOH	StS	I	I/Q	12	14.0	=	3	+
Maurer, 2004[54]	111	88 (7.0)	82.0	L	cOH	StS	C	MR	9	NR	=	5	−
Maurer, 2005[55]	139	88 (7.0)	85.0	L	NR	StS	C	MR	10	34.0	=	4	−
Ooi, 1997[56]	911	79 (12.1)	80.0	Cs	cOH	AS	I	I/Q	6	51.5	=	4	+

Ooi, 2000[57]	844	>60	81.7	L	cOH	AS	I	Obs	14.4	53.9	+	7	+[†]
Shaw, 2015[58]	46	83 (7.8)	54	Cs	cOH	AS	C	I/Q	12	35	=	4	+
Tinetti, 1986[59]	79	79 (7.0)	68	L	sOH	AS	NR	Obs	3	4	=	4	−
Patients with Parkinson's disease													
François, 2017[6]	17702	74 (11.0)	59.1	Cs	NR	NR	NR	MR	12	20.1	+	2	+
Gray, 2000[60]	118	>40	38.0	L	cOH	NR	NR	D	3	16.4	=	4	+
Kerr, 2010[61]	101	66 (8.2)	32.7	L	NR	NR	NR	D	6	18.1	+	3	+
Koller, 1989[62]	100	67	39.0	Cs	sOH	NR	NR	I/Q	12	5.9	=	2	+
Matinolli, 2009[63]	120	68 (10.1)	33.3	Cs	cOH	AS	I	I/Q	1	52.5	=	4	+
Merola, 2016[64]	121	66 (9.4)	43.0	Cs	cOH	HUT	I	I/Q	6	30.6	+	4	+
Rascol, 2015[65]	672	>67	42.1	Cs	NR	NR	NR	I/Q	1	12.5	+	2	+
Sithinamsuwan, 2010[66]	82	69 (10.3)	70	Cs	cOH	AS	I	MR	NR	40	=	4	+
Patients with specific other diseases													
Azidah, 2012[67,‡]	288	>60	54.2	Cs	cOH	AS	NR	I/Q	12	12.2	+	3	+
Galizia, 2013[68,§]	90	76 (8.0)	88	Cs	cOH	AS	I	I/Q	6	47	+	3	+
Joo, 2002[69,‖]	104	77 (5.4)	69.2	L	sOH	AS	NR	I/Q	5	23.5	=	5	-
Kadir, 2011[70,‡]	131	68 (5.6)	0	Cs	NR	NR	NR	I/Q	12	NR	+	3	+
Shen, 2015[71,¶]	176	77 (6.6)	42.6	Cs	cOH	AS	I	I/Q	12	20.5	=	6	+
Van Hateren, 2012[72,‡]	563	75 (72-79)	52.9	Cs	cOH	AS	I	I/Q	12	24.3	=	4	+
Van Helden, 2007[73,**]	277	67 (50-91)	72.0	L	cOH	AS	I	I/Q	3	12.0	=	5	+

AS, active stand; BP, blood pressure; C, continuous; cOH, OH according to consensus definition; Cs, cross-sectional; D, fall diary; HUT, head up tilt; I, intermittent; iOH, initial OH; I/Q, interview or questionnaire; L, longitudinal; LoS, fall assessment period as long as the length of stay in hospital or nursing home; MR; falls assessed by screening medical record; NOS, study quality on the Newcastle-Ottawa Scale; NR, not reported; Obs, falls assessed by observation; sOH, systolic OH; sOH−, sOH without symptoms; sOH+, sOH with symptoms; StS, sit to stand.

*Age is presented as a mean (standard deviation), median (range), or range.

[†]In the meta-analyses and subgroup analyses, this study was analyzed as cross-sectional because insufficient longitudinal data were available for meta-analysis.

[‡]Patients with type 2 diabetes.

[§]Patients with degenerative joint disease.

[‖]Patients with depressive disorder.

[¶]Patients with hypertension.

**Patients with a fracture.

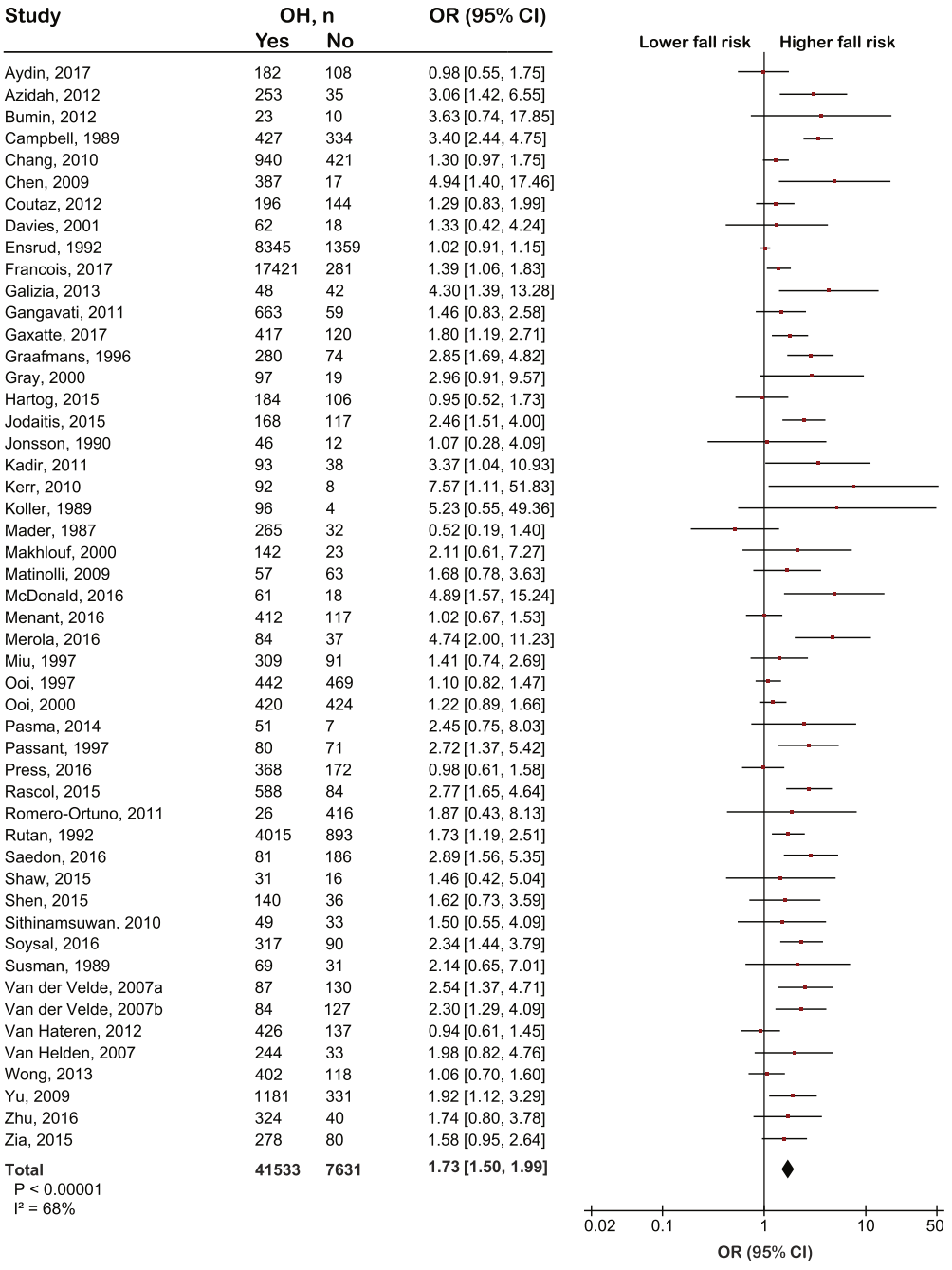

Fig. 2. Forest plot of the meta-analysis of the association between OH and falls.

Furthermore, the association of OH with falls in longitudinal studies, which tested for OH at baseline and assessed falls during follow up, suggests OH being the cause rather than a consequence of falls. In patients with OH, a common neural degenerative process might underlie the association between OH and falls, as PD both affects the autonomic system, causing OH, and the dopaminergic neurons in the nigrostriatal system, causing postural instability.[76,77]

In the subgroup analysis for blood pressure measurement method, the association between OH and falls was strongest in the subgroup of studies using continuous blood pressure measurements, suggesting that testing OH using this method has the largest clinical relevance. This is in line with a previous study which reported that OH and iOH assessed using beat-to-beat continuous blood pressure measurement had a higher sensitivity and association with balance performance than OH assessed using intermittent blood pressure measurements 1 and 3 minutes after postural change.[14] These findings suggest that continuous blood pressure measurements might potentially be useful to identify patients with OH, in whom balance performance responds positively to OH treatment, advocating the use of continuous blood pressure measurements in clinical practice.

The evidence for OH treatment efficacy to prevent falls is circumstantial as no clinical trial assessing the effect of OH treatment on falls is available. Two randomized controlled trials demonstrated an improvement of OH symptoms in patients with neurogenic OH and patients with PD after treatment with midodrine and droxidopa, respectively.[78,79] Two cohort studies found an improvement of gross motor and balance function and symptoms in patients with PD.[80,81]

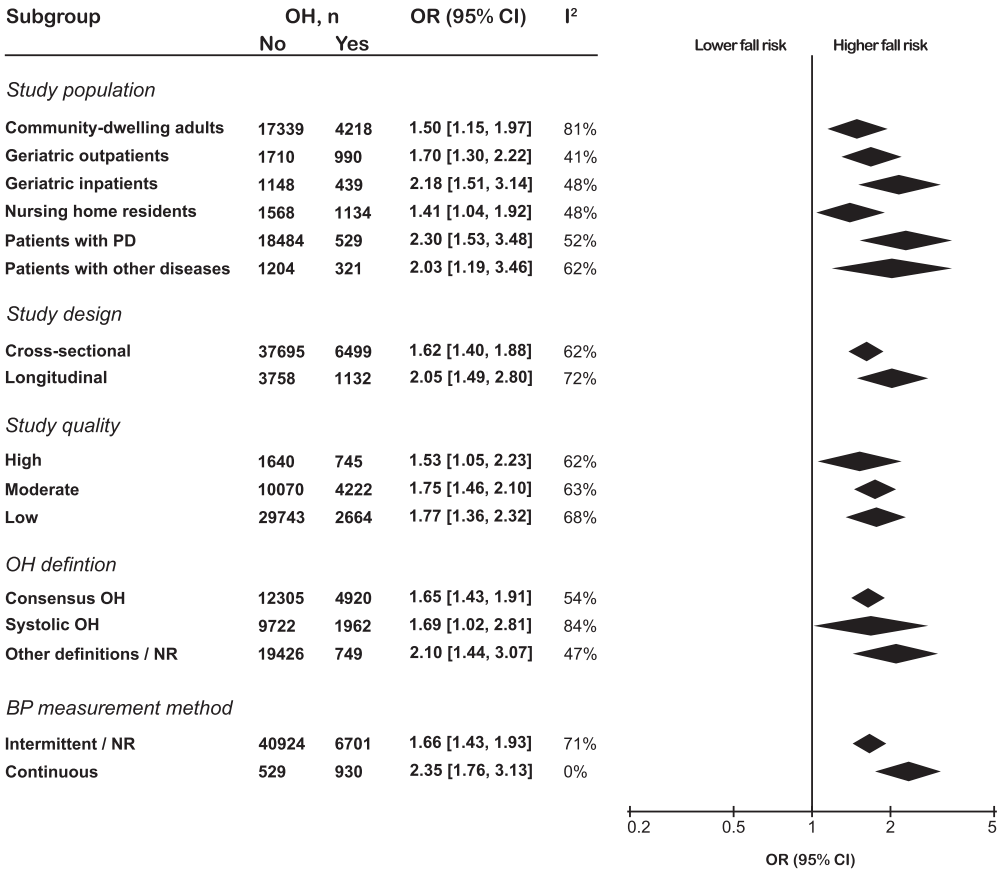

Fig. 3. Forest plot of the subgroup analyses of the association between OH and falls for study population, study design, study quality, OH definition, and blood pressure measurement method. (NR, not reported.)

These studies and the results of the present study suggest OH treatment may be effective to reduce falls, but future studies are needed to address this issue.

Clinical Implications

The results highlight the clinical relevance of blood pressure measurements before and after postural change in a variety of populations of older adults and indicate OH as a potential predictor of falls. It should be tested if OH treatment is beneficial to reduce falls.

Strengths and Limitations

The main strength of this review was the large number of included studies and diverse populations of individuals. These large numbers enabled subgroup analyses for study population, study design, study quality, OH definition, and blood pressure measurement method. However, adjustment for potential confounders was limited, as insufficient studies adjusted for age, sex, and other potential confounders to perform separate meta-analyses. Furthermore, most studies were of moderate or low quality, and no conclusions can be drawn about any causal relationship between OH and falls.

Conclusions and Relevance

OH was positively associated with falls in older adults, independent of study population, study design, study quality, OH definition, and blood pressure measurement method. These results underpin the clinical importance of orthostatic blood pressure measurements in older adults and suggest the use of continuous blood pressure monitors. Furthermore, the association between OH and falls highlights the need to investigate if OH treatment reduces falls.

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Supplementary Data

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.jamda.2018.11.003

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Supplementary Material 1. Search strategy

Medline Search Strategy

Database: MEDLINE (1946 to Present including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and MEDLINE Daily)
Search Strategy:
————————————————————

1 exp Hypotension, Orthostatic/ (5281)
2 ((hypotension adj3 postural) or (postural adj3 blood adj2 pressure) or (orthostatic adj3 blood adj2 press*) or (orthostatic adj3 hypotens*) or orthostasis).kf. (407)
3 ((hypotension adj3 postural) or (postural adj3 blood adj2 pressure) or (orthostatic adj3 blood adj2 press*) or (orthostatic adj3 hypotens*) or orthostasis).tw. (6866)
4 or/1-3 (9329)
5 (Excercise* or (Physical adj2 performanc*) or (Physical adj2 mobilit*) or (Physical adj2 enduranc*) or (Physical adj2 fitness*) or (Walk* adj2 test*) or strength* or gait* or (Postural adj2 balanc*) or (stand* adj2 balanc*) or (balanc* adj2 test*) or (Balanc* adj2 impairment*) or (Activities adj2 daily adj2 liv*) or (stand* adj2 test*) or (Time* up adj2 go test*) or (Activit* adj2 daily adj2 life) or comprehensive geriatric assessment* or (geriatric evaluation adj2 management*) or frail* or fall*).tw. (585748)
6 (Excercise* or (Physical adj2 performanc*) or (Physical adj2 mobilit*) or (Physical adj2 enduranc*) or (Physical adj2 fitness*) or (Walk* adj2 test*) or strength* or gait* or (Postural adj2 balanc*) or (stand* adj2 balanc*) or (balanc* adj2 test*) or (Balanc* adj2 impairment*) or (Activities adj2 daily adj2 liv*) or (stand* adj2 test*) or (Time* up adj2 go test*) or (Activit* adj2 daily adj2 life) or comprehensive geriatric assessment* or (geriatric evaluation adj2 management*) or frail* or fall*).kf. (20955)
7 exp exercise/ or exp exercise test/ or exp exercise tolerance/ or exp physical endurance/ or exp physical fitness/ or exp walk test/ or exp muscle strength/ or exp hand strength/ or exp gait/ or exp postural balance/ or exp "activities of daily living"/ or exp geriatric assessment/ or exp frail elderly/ or exp Accidental Falls/ (345254)
8 or/5-7 (846790)
9 4 and 8 (1695)
10 exp Hypotension, Orthostatic/ (5281)
11 ((hypotension adj3 postural) or (postural adj3 blood adj2 pressure) or (orthostatic adj3 blood adj2 press*) or (orthostatic adj3 hypotens*) or orthostasis).kf. (407)
12 ((hypotension adj3 postural) or (postural adj3 blood adj2 pressure) or (orthostatic adj3 blood adj2 press*) or (orthostatic adj3 hypotens*) or orthostasis).tw. (6866)
13 or/10-12 (9329)
14 (Excercise* or (Physical adj2 performanc*) or (Physical adj2 mobilit*) or (Physical adj2 enduranc*) or (Physical adj2 fitness*) or (Walk* adj2 test*) or strength* or gait* or (Postural adj2 balanc*) or (stand* adj2 balanc*) or (balanc* adj2 test*) or (Balanc* adj2 impairment*) or (Activities adj2 daily adj2 liv*) or (stand* adj2 test*) or (Time* up adj2 go test*) or (Activit* adj2 daily adj2 life) or comprehensive geriatric assessment* or (geriatric evaluation adj2 management*) or frail* or fall*).tw. (585748)
15 (Excercise* or (Physical adj2 performanc*) or (Physical adj2 mobilit*) or (Physical adj2 enduranc*) or (Physical adj2 fitness*) or (Walk* adj2 test*) or strength* or gait* or (Postural adj2 balanc*) or (stand* adj2 balanc*) or (balanc* adj2 test*) or (Balanc* adj2 impairment*) or (Activities adj2 daily adj2 liv*) or (stand* adj2 test*) or (Time* up adj2 go test*) or (Activit* adj2 daily adj2 life) or comprehensive geriatric assessment* or (geriatric evaluation adj2 management*) or frail* or fall*).kf. (20955)
16 exp exercise/ or exp exercise test/ or exp exercise tolerance/ or exp physical endurance/ or exp physical fitness/ or exp walk test/ or exp muscle strength/ or exp hand strength/ or exp gait/ or exp postural balance/ or exp "activities of daily living"/ or exp geriatric assessment/ or exp frail elderly/ or exp Accidental Falls/ (345254)
17 or/14-16 (846790)
18 13 and 17 (1695)

PubMed Search Strategy

1 (((((((((postural hypotension[Other Term]) OR postural blood pressure[Other Term]) OR orthostatic hypotension[Other Term]) OR orthostatic blood pressure[Other Term]) OR orthostasis[Other Term])))) OR ((((((postural hypotension[Title/Abstract]) OR postural blood pressure[Title/Abstract]) OR orthostatic hypotension[Title/Abstract]) OR orthostatic blood pressure[Title/Abstract]) OR orthostasis[Title/Abstract]))) OR "Hypotension, Orthostatic"[mesh] (9146)
2 ((((((postural hypotension[Other Term]) OR postural blood pressure[Other Term]) OR orthostatic hypotension[Other Term]) OR orthostatic blood pressure[Other Term]) OR orthostasis[Other Term])) (245)
3 (((((postural hypotension[Title/Abstract]) OR postural blood pressure[Title/Abstract]) OR orthostatic hypotension[Title/Abstract]) OR orthostatic blood pressure[Title/Abstract]) OR orthostasis[Title/Abstract]) (6694)
4 1 OR 2 OR 3
5 ((((((((((((exercise[MeSH Terms]) OR exercise test[MeSH Terms]) OR exercise tolerance[MeSH Terms]) OR physical endurance[MeSH Terms]) OR physical fitness[MeSH Terms]) OR walk test[MeSH Terms]) OR muscle strength[MeSH Terms]) OR hand strength[MeSH Terms]) OR gait[MeSH Terms]) OR postural balance[MeSH Terms]) OR activities of daily living [MeSH Terms]) OR geriatric assessment[MeSH Terms]) OR frail elderly[MeSH Terms]) OR Accidental Falls[MeSH Terms] (339711)
6 ((((((((((((((((((((Exercise[Other Term] OR Exercises[Other Term]) OR Physical performance[Other Term]) OR Physical mobility[Other Term]) OR Physical endurance[Other Term]) OR Physical fitness[Other Term]) OR walk test[Other Term] OR walk tests[Other Term]) OR strength[Other Term]) OR gait [Other Term] gaits[Other Term]) OR postural balance[Other Term] OR postural balances[Other Term]) OR standing balance [Other Term]) OR balance test[Other Term] OR balance tests [Other Term]) OR balance impairment[Other Term]) OR activity of daily living[Other Term] OR activity of daily life[Other Term] OR activities of daily living[Other Term] OR activities of daily life[Other Term]) OR standing test[Other Term] OR standing tests[Other Term]) OR timed up and go test[Other Term] OR timed up and go tests[Other Term])) OR comprehensive geriatric assessment[Other Term]) OR geriatric evaluation and management[Other Term]) OR frail[Other Term] OR frailty [Other Term]) OR fall[Other Term] OR falls[Other Term]) (5411)
7 ((((((((((((((((((((Exercise[Title/Abstract] OR Exercises[Title/Abstract]) OR Physical performance[Title/Abstract]) OR Physical mobility[Title/Abstract]) OR Physical endurance[Title/Abstract]) OR Physical fitness[Title/Abstract]) OR walk test[Title/Abstract] OR walk tests[Title/Abstract]) OR strength[Title/Abstract]) OR gait[Title/Abstract] gaits[Title/Abstract]) OR postural balance[Title/Abstract] OR postural balances[Title/

Abstract]) OR standing balance[Title/Abstract]) OR balance test [Title/Abstract] OR balance tests[Title/Abstract]) OR balance impairment[Title/Abstract]) OR activity of daily living[Title/Abstract] OR activity of daily life[Title/Abstract] OR activities of daily living[Title/Abstract] OR activities of daily life[Title/Abstract]) OR standing test[Title/Abstract] OR standing tests[Title/Abstract]) OR timed up and go test[Title/Abstract] OR timed up and go tests[Title/Abstract])) OR comprehensive geriatric assessment[Title/Abstract]) OR geriatric evaluation and management[Title/Abstract]) OR frail[Title/Abstract] OR frailty[Title/Abstract]) OR fall[Title/Abstract] OR falls[Title/Abstract]) (161461)

8 5 OR 6 OR 7 (464972)

9 4 AND 8 (1429)

Embase Search Strategy

1 exp falling/ (32186)

2 exp orthostatic hypotension/ or exp orthostatic stress/ or exp orthostatic blood pressure/ (19527)

3 ((hypotension adj3 postural) or (postural adj3 blood adj2 pressure) or (orthostatic adj3 blood adj2 press*) or (orthostatic adj3 hypotens*) or orthostasis).kw. (1449)

4 ((hypotension adj3 postural) or (postural adj3 blood adj2 pressure) or (orthostatic adj3 blood adj2 press*) or (orthostatic adj3 hypotens*) or orthostasis).tw. (9595)

5 or/2-4 (22485)

6 exp physical performance/ or exp physical mobility/ or exp "physical activity, capacity and performance"/ or exp exercise/ or exp exercise test/ or exp body equilibrium/ or exp endurance/ or exp fitness/ or exp hand strength/ or exp muscle strength/ or exp grip strength test/ or exp balance impairment/ or exp daily life activity/ or exp activity of daily living assessment/ or exp geriatric assessment/ or exp frail elderly/ or exp falling/ (994777)

7 (Excercise* or (Physical adj2 performanc*) or (Physical adj2 mobilit*) or (Physical adj2 enduranc*) or (Physical adj2 fitness*) or (Walk* adj2 test*) or strength* or gait* or (Postural adj2 balanc*) or (stand* adj2 balanc*) or (balanc* adj2 test*) or (Balanc* adj2 impairment*) or (Activities adj2 daily adj2 liv*) or (stand* adj2 test*) or (Time* up adj2 go test*) or (Activit* adj2 daily adj2 life) or comprehensive geriatric assessment* or (geriatric evaluation adj2 management*) or frail* or fall*).tw. (718598)

8 (Excercise* or (Physical adj2 performanc*) or (Physical adj2 mobilit*) or (Physical adj2 enduranc*) or (Physical adj2 fitness*) or (Walk* adj2 test*) or strength* or gait* or (Postural adj2 balanc*) or (stand* adj2 balanc*) or (balanc* adj2 test*) or (Balanc* adj2 impairment*) or (Activities adj2 daily adj2 liv*) or (stand* adj2 test*) or (Time* up adj2 go test*) or (Activit* adj2 daily adj2 life) or comprehensive geriatric assessment* or (geriatric evaluation adj2 management*) or frail* or fall*).kw. (53323)

9 or/6-8 (1523611)

10 5 and 9 (5009)

Supplementary Material 2. Newcastle-Ottawa Scale (NOS)

Specified NOS Scale

Note: A study can be given a maximum of 1 star for each numbered item within the Selection and Outcome categories. A maximum of 2 stars can be given for comparability.

Selection

1. Representativeness of the exposed cohort with orthostatic hypotension
   a. Subjects representative of the average subject aged 65 years and older with orthostatic hypotension*
   b. Not representative or no description
2. Selection of the nonexposed cohorts: subjects without orthostatic hypotension from the same community
   a. Yes*
   b. No
   c. No description of the derivation of the nonexposed cohort
3. Ascertainment of exposure: how was the orthostatic hypotension diagnosis made
   a. Blood pressure was measured both continuously and intermittently*
   b. Blood pressure was measured continuously*
   c. Blood pressure was measured intermittently
   d. No description or unclear
4. How was orthostatic hypotension defined?
   a. Based on widely accepted definition of OH*
   b. Other
   c. Not specified

Comparability

5. Adjustment for age and sex
   a. The study adjusts for age or sex*
   b. The study does not adjust for age or sex
6. Adjustment for other confounders
   c. The study adjusts for other factors: medication (eg, antihypertensives, ACE inhibitors, beta-blockers), comorbidities (eg, Parkinson), etc.*
   d. The study does not adjust for other factors

Outcome

7. Assessment of falls outcome
   a. Observed by physician or self-reported prospective*
   b. Self-reported retrospective
   c. No description
   d. Other
8. Was follow-up long enough for fall outcomes to occur
   e. Yes, >6 months*
   f. No, <6 months
   g. No follow-up in article
9. Adequacy of follow-up of cohorts
   h. Complete follow-up, with all subjects accounted for*
   i. Subjects lost to follow up unlikely to introduce bias—number lost is less than or equal to 20% or description of those lost suggested no difference from those followed*
   j. Follow-up rate less than 80% and on description of those lost
   k. Not described or not applicable

* One point.

Supplementary Material 3
NOS score per study

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Score
Community-dwelling adults										
Campbell, 1989[1]	*	*					*	*	*	5
Chang, 2010[2]	*	*		*	*	*				5
Ensrud, 1992[3]	*	*			*					3
Gangavati, 2011[4]	*	*			*	*	*	*	*	7
Heitterachi, 2002[5]	*	*	*				*	*	*	6
Kario, 2001[6]	*						*	*	*	4
Liu, 1995[7]	*			*			*	*	*	5
Lord, 1995[8]	*						*	*	*	4
Mader, 1987[9]	*	*					*			3
McDonald, 2016[10]	*	*	*	*			*	*	*	7
Menant, 2016[11]	*	*		*	*		*	*	*	7
Romero-Ortuno, 2011[12]	*	*	*	*			*			5
Rutan, 1992[13]	*	*		*	*	*				5
Wong, 2013[14]	*	*		*			*	*	*	6
Yu, 2009[15]	*	*								2
Zhu, 2016[16]	*	*		*						3
Zia, 2015[17]	*	*		*	*	*				5
Geriatric outpatients										
Allan, 2009[18]	*	*	*		*	*	*	*	*	8
Aydin, 2017[19]	*	*		*			*			4
Blumenthal, 1980[20]	*									1
Davies, 2001[21]	*	*	*				*		*	5
Gaxatte, 2017[22]	*	*		*			*	*		5
Miu, 1997[23]	*	*								2
Pasma, 2014[24]	*		*	*	*		*			5
Press, 2016[25]	*	*		*						3
Saedon, 2016[74]	*	*	*	*	*	*				6
Susman, 1989[75]	*	*		*						3
Van der Velde, 2007[27]	*	*	*	*						4
Van der Velde, 2007[31]	*	*	*	*	*	*	*		*	8
Geriatric inpatients										
Chen, 2009[63]	*	*		*			*			4
Coutaz, 2012[76]	*	*		*			*			4
Jodaitis, 2015[77]	*	*		*		*				4
Passant, 1997[78]	*	*				*				3
Soysal, 2016[79]	*	*		*			*			4
Nursing home residents										
Bumin, 2002[80]	*	*								2
Graafmans, 1996[81]	*	*		*	*		*	*		6
Gray-Miceli, 2016[26]	*	*		*						3
Hall, 2015[28]	*				*	*				3
Hartog, 2015[29]	*			*	*	*				4
Hartog, 2017[30]	*			*	*	*	*	*	*	7
Jonsson, 1990[32]	*		*							2
Makhlouf, 2000[33]	*	*		*						3
Maurer, 2004[34]	*		*				*	*	*	5
Maurer, 2005[35]	*		*					*	*	4
Ooi, 1997[36]	*	*		*		*				4
Ooi, 2000[37]	*	*		*		*	*	*	*	7
Shaw, 2015[38]	*	*	*	*						4
Tinetti, 1986[39]	*	*					*		*	4
Patients with Parkinson's disease										
François, 2017[40]	*	*					2			
Gray, 2000[41]	*	*					*		*	4
Kerr, 2010[42]	*						*	*		3
Koller, 1989[43]	*	*								2
Matinolli, 2009[44]	*	*		*			*			4
Merola, 2016[45]	*	*		*			*			4
Rascol, 2015[46]	*	*								2
Sithinamsuwan, 2010[47]	*	*		*			*			4
Patients with specific other diseases										
Azidah, 2012[48]	*	*		*						3
Galizia, 2013[49]	*	*		*						3
Joo, 2002[50]	*				*	*	*		*	5
Kadir, 2011[51]	*				*	*				3
Shen, 2015[52]	*	*		*	*	*	*			6
Van Hateren, 2012[53]	*			*	*	*				4
Van Helden, 2007[54]	*	*		*			*		*	5

*Attributed point.

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